Clinical Management Review

Severe Asthma in Children

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

Target Audience: Physicians and researchers within the field of allergic disease.

Accreditation/Provider Statements and Credit Designation: The American Academy of Allergy, Asthma & Immunology (AAAAI) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians. The AAAAI designates these educational activities for a maximum of 1 AMA PRA Category 1 Credit. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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Activity Objectives

1. To identify how severe asthma in children is defined and how it differs from adults
2. To discuss how to evaluate a child with this disease and consider important comorbidities and other conditions that can have similar symptoms
3. To consider evidence-based management of a child with severe asthma

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: T. Guilbert is on the American Board of Pediatrics and the Pediatric Pulmonary Subboard; has received consultancy fees from Teva, GlaxoSmithKline, and Regeneron Pharmaceuticals; has received research support from the Centers for Disease Control, Department of Health and Human Services (DHHS FAB 20166; T72 MC00008-20-00), National Institutes of Health (NIH), University of Wisconsin Madison Medical and Education Research Committee, Teva, GlaxoSmithKline/Development Limited, CF Foundation Therapeutics, Roche/Genentech, and the NIH; receives royalties from UpToDate; and has received payment for development of educational presentations from Teva. L. B. Bacharier has received consultancy fees from Aerocrine, GlaxoSmithKline, Genentech/Novartis, Merck, Schering, Cephalon, and DBV Technologies; has received research support from the National Heart, Lung, and Blood Institute (NHLBI)/NIH AsthmaNet (NHLBI U10 HL098090; U10 HL109168; P01 HL070831); has received lecture fees from Aerocrine, AstraZeneca, Genentech/Novartis, GlaxoSmithKline, Merck, and Schering. A. M. Fitzpatrick has received research support from the NIH, NHLBI (R01 NR012021) and National Institute of Nursing Research (R01 NR013700); has received consultancy fees from MedImmune, Merck Scientific Advisory Board, GlaxoSmithKline Advisory Board, Genentech, and Boehringer Ingelheim.

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Abbreviations used
ACQ- Asthma Control Questionnaire
ACT- Asthma Control Test
ATS- American Thoracic Society
BMI- Body mass index
CT- Computed tomography
EGD- Esophagogastroduodenoscopy
ERS- European Respiratory Society
FENO- Exhaled nitric oxide
FVC- Forced vital capacity
GERD- Gastroesophageal reflux disease
GINA- Global Initiative on Asthma
ICS- Inhaled corticosteroid
LABA- long-acting β-agonist
N/A- Not available
NAEPP- National Asthma Education and Prevention Program
PEF- Peak expiratory flow

Severe asthma in children is characterized by sustained symptoms despite treatment with high doses of inhaled corticosteroids or oral corticosteroids. Children with severe asthma may fall into 2 categories, difficult-to-treat asthma or severe therapy-resistant asthma. Difficult-to-treat asthma is defined as poor control due to an incorrect diagnosis or comorbidities, or poor adherence due to adverse psychological or environmental factors. In contrast, treatment resistant is defined as difficult asthma despite management of these factors. It is increasingly recognized that severe asthma is a highly heterogeneous disorder associated with a number of clinical and inflammatory phenotypes that have been described in children with severe asthma. Guideline-based drug therapy of severe childhood asthma is based primarily on extrapolated data from adult studies. The recommendation is that children with severe asthma be treated with higher-dose inhaled or oral corticosteroids combined with long-acting β-agonists and other add-on therapies, such as antileukotrienes and methylxanthines. It is important to identify and address the influences that make asthma difficult to control, including reviewing the diagnosis and removing causal or aggravating factors. Better definition of the phenotypes and better targeting of therapy based upon individual patient phenotypes is likely to improve asthma treatment in the future. **(J Allergy Clin Immunol Pract 2014;2:489-500)**

Key words: *Childhood severe asthma; Childhood difficult-to-treat asthma; Severe asthma phenotypes; Childhood severe asthma treatment; Review*

Asthma is the most common chronic lung disease of childhood, which affects >6.6 million children in the United States.[1] Most children with asthma achieve good symptom control when treated with low-to-medium doses (<500 mcg/d fluticasone equivalents) of inhaled corticosteroids (ICS). However, severe asthma in children is characterized by sustained symptoms despite treatment with high doses of ICS or oral corticosteroids[2,3] and represents approximately 5% of childhood asthma cases.[4] Although this form of asthma is the least common, it accounts for nearly 50% of all asthma-related expenditures.[5,6] It has been suggested that children with severe asthma may fall into 2 categories, difficult-to-treat asthma or severe therapy-resistant asthma. Difficult-to-treat asthma is defined as poor control due to an incorrect diagnosis or comorbidities or poor adherence due to adverse psychological or environmental factors. In contrast, treatment resistant is defined as difficult asthma despite management of these factors.[7] Analysis of data indicates that children with severe asthma begin to demonstrate symptoms early in life and that the majority have atopy and reversible airway obstruction.[8,9] Although these data have helped define the scope of this disease in children, there are numerous questions left unanswered. This review will focus on severe asthma in school-age children (range, 5-17 years), from definition to management.

SEVERE ASTHMA IN CHILDREN IS DIFFERENT THAN ADULT DISEASE

Extrapolating adult severity classifications to children is difficult for a number of reasons. Adults with asthma are more likely to exhibit a persistent pattern, whereas children may have a pattern of rapidly evolving, frequent, and often severe exacerbations. Children have severe exacerbations triggered by viral infections and/or allergen exposure that can result in health care utilization but then often remain asymptomatic between these episodes.[10,11] Phenotypes of severe asthma in children differ from those of adults and change more rapidly. It, therefore, is necessary to reassess phenotypes at regular intervals. Responses to medications[12] and the more pronounced growth and bone maturation adverse effects of ICS[13] also differ between childhood and adult asthma. Lung function measurements also show different patterns, are age-dependent, and may be within normal limits despite significant symptom burden and medication use.[14-16] The distal airways are more affected, and increased distal lung resistance, in the absence of significant large airway involvement, likely explains the often unimpaired FEV_1 values.[17] Furthermore, other measures of lung function, such as FEV_1 per forced vital capacity, forced expiratory flow at 25% to 75% of forced vital capacity predicted, or the degree of airway responsiveness to bronchodilators may relate better to asthma severity.[15] Children, particularly boys, demonstrate more hyperinflation with increased residual volume and total lung capacity.[18] Girls with severe asthma also exhibit some air-trapping and airflow limitation during bronchodilator abstinence but to a lesser magnitude than seen with boys, and this finding is generally reversible with bronchodilation.[19]

Results of epidemiology studies indicate that children with atopic asthma have a slow decline in lung function over time.[14,20,21] This decline in lung function may be accelerated in children with severe asthma. Children with severe asthma typically are more atopic, with higher serum IgE levels and demonstrate reversible airway obstruction compared with their adult counterparts. Children with severe asthma are differentiated by higher exhaled nitric oxide (FENO), higher IgE and eosinophil levels, and differential patterns of sensitization to aeroallergens, especially molds.[3] Severe asthma may be due to underlying severity of the disease from persistent airway inflammation and relative corticosteroid insensitivity,[22-24] or poor asthma control due to a number of biologic, environmental, and/or social factors.[7,25,26] Adolescents are at an increased risk of a higher prevalence of severe asthma and death from asthma due to reduced adherence to treatment and increased risk-taking behaviors (smoking, illicit drug use). Poor adherence also is associated with complex treatment regimens, familial strain, inadequate supervision of the child, and possible secondary gains linked to poorly controlled asthma.[27] Poor asthma control may be